Executive Summary

Systematic Literature Review and Meta-Analyses on Birth Spacing: How Birth Spacing Relates to Infant and Child Mortality, Maternal and Perinatal Health, and Maternal and Child Nutrition Outcomes.

CATALYST Consortium
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OBJECTIVE

To clarify and refine international recommendations on the Optimal Birth Spacing Interval (OBSI), CATALYST, in consultation with USAID, UNICEF, and WHO, commissioned three wide-ranging studies in 2004. Using the rigorous guidelines, these studies considered all available evidence regarding the association of birth intervals with: Infant and child mortality; Maternal and perinatal health; and Maternal and child nutrition outcomes. This paper summarizes the findings from the following three studies:

1. SYSTEMATIC LITERATURE REVIEW AND META-ANALYSIS OF THE RELATIONSHIP BETWEEN INTERPREGNANCY OR INTERBIRTH INTERVALS AND INFANT AND CHILD MORTALITY (Rutstein, Johnson, & Conde-Agudelo 2004).

2. EFFECT OF BIRTH SPACING ON MATERNAL AND PERINATAL HEALTH: A SYSTEMATIC REVIEW AND META-ANALYSIS (Conde-Agudelo 2004)

3. BIRTH SPACING LITERATURE: MATERNAL AND CHILD NUTRITION OUTCOMES (Dewey & Cohen 2004)

This report introduces these three new studies as the most up-to-date information on birth spacing and the optimal birth spacing interval. These new studies have confirmed much of the child-health research that led to the CATALYST's optimal birth-spacing initiative, while challenging some previous nutrition and maternal-health assumptions. So that results may inform international birth-spacing guidelines, USAID and WHO Expert Panels are reviewing all of the final reports for technical quality, methodological soundness, and usefulness. The findings from this research can inform guidelines on birth spacing and provide insight into improving reproductive health and family planning services, counseling and outreach programs.

Systematic literature reviews (SLRs) describe the current studies, and are an essential step in any research process to describe what work has been done on a topic and

summarize the knowledge. However, even a systematic literature review does not have the capacity to reflect the sum of the findings with statistical significance nor predict probability of future events; it is only descriptive. Therefore, meta-analyses were done where there was adequate data to analyze collectively and draw conclusions from the results. The meta-analyses can discern if there is an association between birth spacing and selected maternal and child outcomes, as well as draw conclusions and make research-based recommendations about an optimal birth spacing interval.

METHODS

Meta-analyses are the "gold standard" from which policy and program decisions can be made. Most meta-analysis studies analyze the data from randomized controlled trials (RCTs) using the rigorous Cochrane review guidelines, and the findings are used to inform and support the practice of evidence-based medicine. However, because of the nature of the topic, most studies on birth spacing are observational in nature and do not involve any RCTs. Still, the meta-analysis of observational studies has been shown to be a powerful tool. To make the results useful and scientifically valid, the "MOOSE" guidelines[1] for meta-analysis of observational studies were used, wherein strict protocols are followed to control for confounding factors, minimize bias and standardize the collection, analysis, and reporting of results.

To locate the appropriate literature for review, publications from 1981 through 2004 in seven electronic databases: MEDLINE, POPLINE, EMBASE, CINAHL, LILACS, ECLA, and DEC were searched for birth spacing as a major topic/heading and outcomes for three major areas including, pregnancy, infants and children, and maternal health. In addition to the various health databases, the researchers carried out a search in review articles, proceedings of several international meetings on birth spacing, bibliographies of the retrieved articles, reviews, and chapters in standard textbooks on birth spacing. Over 1,000 articles were scanned and reviewed.

No language restrictions were imposed. Articles in English, Spanish, French, and Serb were included. The investigators also used the "snowball" method, by checking the references cited in review papers and the articles identified through the search engines, to

find additional relevant (published and unpublished papers) both before and after 1980. To find unpublished studies, relevant researchers in the field were contacted.

On the basis of this exhaustive search, 470 articles and reports were retrieved, evaluated, and classified. All abstracts identified by the search were read and categorized according to whether or not the study had (or might have) data relevant to the outcomes of interest. The full papers for all relevant aspects were obtained for further review. These papers were then categorized into those that actually did or did not have data on the outcomes of interest. Case studies, editorials, and review papers that did not report primary data were in the latter category.

Studies were included in our systematic review if they met the following minimal criteria: 1) Study design: observational cohort, cross-sectional, case-control studies; 2) Statistical analysis: maternal age and socioeconomic status were considered to be the most important confounding variables because socioeconomic status and place or areas of residence influence access to health services for both family planning and prenatal and maternal care, which could produce a spurious relationship between intervals and outcomes; 3) Exposure: the definition of interpregnancy interval corresponded to the period between the delivery of the previous infant (or the end of the previous pregnancy by miscarriage or abortion) and the conception of the current pregnancy, typically measured as the date of the last menstrual period. Although the use of birth-to-birth interval overestimates the risks for very short intervals, studies using birth-to-birth interval were also included and analyzed separately; and (4) Outcome measures: the adverse health and nutritional outcomes enumerated for the study as a primary or secondary outcome.

Studies were excluded from the systematic review if they were case series or reports, editorials, letters to the editor or reviews; or if they exclusively used univariate analysis; or if they did not adjust for at least maternal age and for socioeconomic status; or if they did provide data.

Studies were also included in the meta-analyses if they met the following criteria: 1) provided data for three or more interval strata; and 2) provided unadjusted odds ratios or the necessary information to construct a 2 x 2 table and calculate it and its 95% confidence intervals or provided adjusted odds ratios or regression coefficients *b*. Studies

were excluded from the meta-analysis if risk estimates or confidence intervals were not published and sufficient information to calculate them could not be obtained.

Studies were excluded from the meta-analysis if they did not divide the interval into categories (e.g., used only as a continuous variable), did not report the number of cases within each interval category, if their results were not able to be put into a 2 x 2 format or involved unique outcomes (e.g., unique mortality age groups).

FINDINGS

1. Birth Spacing and Infant and Child Mortality

Systematic literature review and meta-analysis of the relationship between interpregnancy or interbirth intervals and infant and child mortality (Rutstein, Johnson, & Conde-Agudelo 2004).

For this study, 234 relevant reports were retrieved and evaluated. A total of 65 studies, including more than 1,600,000 live births, met the inclusion criteria for the systematic review. Results varied by age category, with a large proportion of studies reporting statistically significant findings regarding length of birth interval and infant and child mortality. To discern the affect of birth interval length, 28 cohort and cross-sectional studies were adequate for consideration in the meta-analysis of the relationship between birth-to-birth interval and neonatal, post-neonatal, infant, child, and under-five mortality. All studies in the meta-analysis were from developing countries.

The meta-analysis found that the length of the preceding birth interval is highly related to the risk of dying in early childhood, that there is a dose response to interval length, in that the shorter the interval, the higher the risk, and that the effect of birth interval on mortality is not limited to the neonatal period but applies to all age ranges.

The odds ratios by birth interval from the studies eligible for meta-analysis were pooled into three interval groups, less than 18 months, 18 to 36 months, and more than 36 months. The combined odds ratios show that not only does the under 18 month interval have an increased risk of mortality at all ages under five years, but also 18-to-36 month

interval, compared with intervals more than 36 months. Comparisons between the pooled unadjusted and adjusted odds ratios indicate that there is a need to control for confounding factors. The pooled adjusted odds ratios illustrate three important findings: 1) there is a substantially increased risk of dying in early childhood from intervals of 36 months or less; 2) that this increased risk is not primarily concentrated in the neonatal period; and 3) there is a dose response to interval length.

The further analysis of dose response indicates that there is almost a 4% increase in the risk of mortality under age five years for each month that the preceding birth interval is shorter than 36 months. The value of the dose response increases with age, rising from 3.7% per month in the neonatal mortality period to 4.0% in the child (age one-to-four years) mortality period.

Meta-regression curves showed a J-shaped relationship between birth-to-birth interval and children's mortality. For death at ages less than five years, the lowest risk was for intervals longer than 40 months, and the highest risk was for intervals shorter than 15 months. Although risks declined as the birth interval increased, intervals of 15 to 35 months between births were significantly related to increases in risk at all mortality age groups for children less than five years old.

Compared with children with preceding birth-to-birth intervals of 37 or more months, those with intervals shorter than 18 months had an increased risk of neonatal death, post-neonatal mortality, infant, child, and under-five mortality. Intervals of 18 to 36 months were also associated with a significantly greater risk for neonatal, post-neonatal mortality, infant, child, and under-five mortality. There was also some indication of an increased risk of mortality for preceding intervals longer than about 60 months.

2. Birth Spacing and Maternal and Perinatal Health

Effect of birth spacing on maternal and perinatal health: a systematic review and meta-analysis (Conde-Agudelo 2004)

For this study, 170 reports, 57 cohort or cross-sectional and 20 case-control studies, including 12,669,813 pregnancies, met the inclusion criteria for the systematic review. Among them, 26 cohort and cross-sectional studies were considered in the meta-analyses of the relationship between interpregnancy interval and adverse perinatal outcomes. Among these, 14 studies provided data to estimate pooled adjusted odds ratios for the relationship between interpregnancy interval and several adverse outcomes including: preterm birth, low birth weight, and small for gestational age.

Questions of interest were: 1) What is the actual effect of short birth-to-conception intervals on maternal and perinatal health? 2) What is the actual effect of long birth-to-conception intervals on maternal and perinatal health? 3) Is there an optimal birth-to-conception interval in which maternal and perinatal outcomes are best?

The study concluded that the optimal birth-to-conception interval for prevention of these adverse perinatal outcomes is 18 to 59 months. There were no differences in the risk of adverse perinatal outcomes between women with intervals 24 to 59 months and those with 18-23 months.

It was not possible to estimate pooled adjusted odds ratios for the relationship between interpregnancy interval and both fetal and early neonatal death, because the categories of intervals used and the reference categories did not coincide in all studies. The studies on the association between both short and long interpregnancy intervals and the risk of fetal and early neonatal death yielded mixed results. However, long interpregnancy intervals, possibly greater than 59 months, were independently associated with an increased risk of preeclampsia.

The relationship between birth spacing and other adverse maternal outcomes was also inconclusive, because the number of studies meeting the minimal criteria for inclusion in the systematic review was too limited. These outcomes included maternal

death, anemia, premature rupture of membranes, third trimester bleeding, postpartum hemorrhage, and infection.

3. Birth Spacing and Maternal and Child Nutrition Outcomes

Birth spacing literature: maternal and child nutrition outcomes (Dewey & Cohen 2004)

For this study, 246 abstracts were reviewed, among which 27 papers met the inclusion criteria and were included in the summary of findings below (16 for child nutrition, eight for maternal anthropometric status, and three for maternal anemia or iron status). The study examined the association between birth intervals or interpregnancy intervals and their synonyms and the following outcomes for infants and children: growth, nutritional status, stunting, wasting, underweight, and anemia. In addition, the study reviewed the research pertaining to outcomes for women: risk of anemia during pregnancy and during the early and late postpartum period, risk of vitamin A depletion, and risk of maternal depletion. The following questions were the focus of the review: 1) Is a longer interpregnancy interval (previous or subsequent) associated with child nutritional status, i.e., a lower risk of child stunting, wasting, anemia, and poor micronutrient status? 2) Is a longer interpregnancy interval associated with higher maternal weight or body mass index? 3) Is a longer interpregnancy interval associated with a lower risk of maternal anemia or vitamin A deficiency?

The studies on child nutrition outcomes indicated that a longer birth interval of at least 24 months was associated with a lower risk of malnutrition in some populations, but not all. Fifteen studies showed a consistently positive association, i.e., a longer interval (at least 24 months) was associated with better nutritional status, whereas 14 studies showed no significant relationship, and two studies yielded mixed results. In those countries in which the relationship was significant, the reduction in stunting associated with a previous birth interval greater than or equal to 36 months (compared to 24-35 months) was 30-54%. Some of this reduction may be due to residual confounding, i.e., to factors not included in the analysis, such as breastfeeding and maternal health.

There was no clear evidence of an association between interpregnancy interval or recuperative interval and maternal anthropometric status. The studies on maternal anemia also yielded mixed results. One study showed an increased risk for maternal anemia when the interpregnancy interval was less than six months, but the analysis did not control for iron supplementation during pregnancy. The other two studies did not show a significant association between interpregnancy interval and maternal anemia. On the basis of their review, the authors have concluded that a meta-analysis of the health outcomes reviewed is not appropriate.

CONCLUSIONS

Infant and Child Mortality

The findings of the meta-analysis on infant and child mortality strongly support the recommendation of a 3-year interval between births. The pooled adjusted odds ratios illustrate three important findings:

1) There is a substantially increased risk of dying in early childhood from intervals of 36 months or less;
2) This increased risk is not primarily concentrated in the neonatal period; and
3) There is a dose response to interval length.

Compared with children with preceding birth-to-birth intervals of 37 or more months, those with intervals shorter than 18 months had an increased risk of neonatal death, post-neonatal mortality, infant, child, and under-five mortality. Intervals of 18 to 36 months were also associated with a significantly greater risk for neonatal, post-neonatal, infant, child, and under-five mortality. There is almost a 4% increase in the risk of mortality under age five years for each month that the preceding birth interval is shorter than 36 months. There was also some indication of an increased risk of mortality for preceding intervals longer than about 60 months.

Maternal and Perinatal Health

The research on maternal and perinatal health finds that the safest interpregnancy interval, from birth to conception, is from 18 to 59 months. By adding nine months to approximate a full term gestation, this translates to a birth interval of 27 to 59 months. The meta-analyses show that birth to conception intervals shorter than 18 months and longer than 59 months are significantly associated with increased risk of several adverse perinatal outcomes, such as preterm birth, LBW, and SGA. Less clear is the association between both short and long interpregnancy intervals and the risk of fetal and early neonatal death. With regard to the effects of birth spacing on maternal health, it was found that long interpregnancy intervals are associated with an increased risk of preeclampsia.

It was not possible to draw conclusions regarding the relationship between birth spacing and other adverse maternal outcomes such as death, anemia, premature rupture of membranes, third-trimester bleeding, postpartum hemorrhage, and infection because the number of studies meeting the minimal criteria for inclusion in the systematic review was too limited. We concluded the optimal birth to conception interval for preventing adverse perinatal outcomes is 18 to 59 months.

Maternal and Child Nutrition Outcomes

Outcomes for maternal and child nutrition were inconclusive. There was no clear evidence of an association between interpregnancy interval or recuperative interval and maternal anthropometric status. The studies on maternal anemia also yielded mixed results. One study showed an increased risk for maternal anemia when the interpregnancy interval was less than six months, but the analysis did not control for iron supplementation during pregnancy. The other two studies did not show a significant association between interpregnancy interval and maternal anemia. On the basis of their review, the authors have concluded that a meta-analysis of the health outcomes reviewed is not appropriate.

DISCUSSION

The effects of birth spacing on maternal and perinatal health found in this study should furnish a strong motivating force for health personnel and services to provide family planning. The health sector will supply such care not only to those wishing to limit their fertility for personal, social, or economic reasons, but will also provide the needed services to those practicing family planning for health reasons. The results of the systematic review could be used by providers of reproductive health care around the world to advise women who plan to become pregnant after a previous birth on the association between adverse pregnancy outcomes and short and long interpregnancy intervals, and on the benefits of delaying a subsequent pregnancy for approximately two to five years to improve the health of both the mother and the next infant.

In addition, health care providers should advise women who receive antenatal care about the increased risk for several adverse outcomes to both their infants and themselves associated with short and long interpregnancy intervals.

Despite the advancement in understanding the relationship between birth spacing and adverse pregnancy outcomes during the last two decades, little information is available on the effects of birth spacing on maternal morbidity and mortality or the understanding of mechanisms by which birth spacing might improve the health of mothers and their children. Therefore, more research is needed to understand the effects of birth spacing on maternal health. Also, more studies are needed on whether the effects of birth spacing on maternal and perinatal health differ in developed versus developing nations. Finally, it is imperative to understand the causes for both short and long intervals in any population in order to interpret the data on health risks. The consequence of this may be that family planning policies and messages may need to be tailored for different populations.

Future studies should include a large-scale prospective longitudinal design. Additionally studies should:

- Use interpregnancy interval as a measure of birth spacing
- Evaluate the risk of adverse health outcomes over a full range of intervals
- Use stratified and logistic regression analyses to address potential confounding factors
- Involve an adequate sample size
- Follow up on at least 90% of the women originally recruited
- Hold the diagnosis of adverse pregnancy and neonatal outcomes to strict criteria
- Measure intervals and the diagnosis of adverse health outcomes through medical records or direct measurement
- Blind researchers to the measurement of intervals and ascertainment of adverse outcomes
- Provide adjusted estimates of association

Moreover, more studies should focus on addressing several unanswered questions and weaknesses identified in this review such as the effects of birth spacing on maternal and perinatal mortality, the role of breastfeeding and nutritional supply on the associations found, and the mechanisms to explain such associations.

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[1] Stroup DF, Berlin JA, Morton SC, Olkin I, Williamson GD, Rennie D, et al. 2000. Meta-analysis of observational studies in epidemiology (MOOSE). A proposal for reporting. *JAMA*, vol. 283, pp. 2008-12.